Response to Questions from the Institute of Medicine

1. What evidence is there to conclude that there is or is not a threshold effect for cancer, heart disease, adverse reproductive effects or lung disease caused by exposure to tobacco or tobacco smoke, and what is the threshold level, if it exists.

This question may be relevant for people who start smoking and choose to use reduced harm products¹: Is there a chance of lower or negligible risk for disease? This question may also be relevant for people who already smoke and have the intention to switch to reduced harm products: Is there a chance for lower or even negligible risk by switching to already existing or to be developed less harmful cigarettes?

The question can be discussed based on epidemiological and mechanistic grounds, using the data available on the effects of smoking existing cigarette types and conceptual considerations.

The gold standard for the determination of the existence of a threshold in the dose-response relationship of a disease is certainly epidemiology. However, the determination of thresholds requires a reasonable resolution of the dosimeter applied to the dose-response relationship under investigation. In terms of the cigarette smoke dose, epidemiology has been mainly based on the number of cigarettes per day. Most epidemiological studies have used increments of 10 cigarettes per day which is course relative to the current average consumption in the US of 19 cigarettes per day. Though the data is available for finer evaluations.

With the limitations in dose resolution given, the dose-response relationship for lung cancer seems to be compatible with linearity in the lower-dose range (e.g., US DHHS 1982 and 1989; IARC, 1986;). The same holds true for other cancer types that are related to cigarette smoking. For cardiovascular diseases, the dose-response relationship is relatively flat. In particular, the relative risk for ischemic heart disease was reported to be 1.78 for smoking 20 cigarettes per day (meta-analysis by Law et al., 1997). Extrapolating the data from this meta-analysis to the lower dose range with a super-linear convex dose-response relationship suggests a relatively high risk even for smoking few cigarettes per day. A similar pattern can be observed for the coronary heart disease mortality ratios comprised by the US DHHS (1983). For myocardial infarction, however, the US DHHS (1983) reported a supra-linear or concave dose-response relationship; however, the data did not suggest a threshold. For chronic bronchitis and emphysema, with the above-

PM3006856763

capte of whal

¹ The term 'reduced harm products' as it is used here includes novel cigarette types as well as any kind of replacement therapy in combination with a reduced consumption of conventional cigarettes.

mentioned limits of resolution, there is no indication of deviations from linear dose-response relationships (US DHHS, 1984). For reprotoxicological effects, only rough dose-response data are available that generally do not allow any conclusion on the presence or absence of thresholds (e.g., US DHHS, 1980). In conclusion, the current epidemiological methods are not accurate enough to prove or disprove a no-effect threshold for cigarette smoke-related diseases. However, there is overwhelming epidemiological evidence that lower smoke exposure leads to lower risk, whether or not a hypothetical threshold exists.

From a mechanistic point of view, thresholds are generally conceivable. Non-linear dose-response relationships were established for some effects in humans, e.g., radiation-induced sarcoma (Chemelevsky et al., 1986). Consequently, the current paradigm of default linear dose-response relationships in genotoxic carcinogenesis has been questioned (e.g., Purchase, 1998; Zenick and Bogdanffy, 2000; Müller and Kasper, 2000). This seems to be reasonable for mutagenic and more so for clastogenic effects in face of respective detoxification and repair systems. Moreover, for nongenotoxic carcinogenesis and the promotion phase of carcinogenesis, non-linear dose-response relationships without or with thresholds have been conceptually accepted. For instance, the role of cell proliferation in carcinogen-induced tumor formation leading to threshold effects in some target organs was demonstrated in animal models (Poirier and Beland, 1992). The weight of genotoxic versus non-genotoxic events in tobacco smoke-related carcinogenesis, in particular in the lungs, has been discussed. The declining risk with the duration since smoking cessation (Stellman, 1986; US DHHS, 1989) has been taken as strong evidence for a major role of promotion in pulmonary carcinogenesis from smoking.

In contrast to carcinogenic events, for non-carcinogenic events non-linear dose-response relationships, potentially with thresholds, are generally assumed based on the existence of protective and repair systems. The mechanisms underlying these diseases as well as the whether thresholds might be applicable is often less clear than with carcinogenesis. From experimental toxicology, there are some indications for thresholds being involved in these diseases. For example, a threshold was determined for the accumulation of inflammatory polymorphonuclear leukocytes in the lungs of rat subchronically exposed to cigarette mainstream smoke with increasing concentrations of total particulate matter (Kindt et al., unpublished). This assay is considered to be a surrogate marker for the inflammatory changes seen in cigarette smoke-related bronchitis. Another example for a mechanism-based threshold is the oxidative modification of blood lipoproteins in vitro: only after depletion of antioxidant vitamins with increasing smoke concentrations, the oxidative modification of lipoprotein components is initiated (Eiserich at al.,

Circulation 88: 2149-2155 (1993).

1995). Oxidative modification of the low density lipoprotein is considered a critical step in atherosclerosis (McCall and Frei, 1999).

Most non-carcinogenic smoking-related health effects, such as the risk for chronic bronchitis or coronary heart disease, were also found to recover after smoking cessation (US DHHS, 1984 and 1989). For example, the abnormalities found in blood lipid profiles appear to reverse, at least in part, within weeks of smoking cessation (Stubbe et al., 1982). Also, the flow-mediated and endothelium-dependent peripheral arterial vasodilation, which is impaired by smoking, has been reported to be at least partly reversible after smoking cessation (Celermajer et al., 1993).

Conceptually, thresholds most likely exist for a number of mechanistic events in smoking-related diseases. However, practically these diseases develop in multiple stages (e.g., carcinogenesis) or parallel events (e.g., atherosclerosis and thrombosis) which makes it difficult to deduce thresholds for the overall disease outcome. In addition, these processes are triggered by exposure to a complex mixture of constituents, which may interact at various steps within the disease processes.

In summary, mechanistic considerations generally suggest that there are thresholds for smoking-related adverse health effects. However, thresholds or non-linear dose-response relationships have only rarely been determined in epidemiological studies on cigarette smoking-related diseases, which can be related to the complex exposure and the complex disease processes as well as to the rough dosimetry employed. Nevertheless, since all these effects are dose-dependent and the risks for many of them are reduced upon cessation of smoking, reduced exposure to the smoke constituents related to these effects are considered advantageous regardless of the presence of thresholds.

Dose response 35 trend.

References a Safe (evel of anothing? - yes

Celermajer, D.S., Sorensen, K.E., Georgakopoulos, D. et al.,

Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults.

Chemelevsky, D., Kellerer, A.M., Spiess, H., and Mays, C.W., A proportional hazards analysis of bone sarcoma rates in German radium-224 patients, IN: The Radiobiology of Radium and Thorotrast (Gossner, W., and Gerber, G.B., eds.), Urban and Schwarzenberg, Munich, 1986.

Eiserich, J.P., van der Vliet, A., Handelman, G.J., Halliwell B., and Cross, C.E., tools to meseure this (sofe) - her use our appeals from a MSK reduction PM3006856765 ක්දය ් ලි

HEREFERT PRIORITY

Dietary antioxidants and cigarette smoke-induced biomolecular damage: a complex interaction. Am. J. Clin. Nutr. 62: 1490S-1500S (1995).

International Agency for Research on Cancer (IARC),

Tobacco Smoking, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 38, Lyon 1986.

Law, M.R., Morris, J.K., and Wald, N.J.,

Environmental tobacco smoke exposure and ischemic heart disease; an evaluation of the evidence.

Br. Med. J. 315; 973-980 (1997).

McCall, M.R., and Frei, B.,

Can antioxidant vitamins materially reduce oxidative damage in humans? Free Rad. Biol. Med. 26: 1034-1053 (1999).

Müller, L., and Kasper, P.,

Human biological relevance and the use of threshold-arguments in regulatory genotoxicity assessment: experience with pharmaceuticals.

Mutat. Res. 464: 19-34 (2000).

Poirier, M.C., and Beland, F.A.,

DNA adduct measurement and tumor incidence during chronic carcinogen exposure in animal models: Implications for DNA adduct-based human cancer risk assessment, Chem. Res. Toxicol. 5: 749-755 (1992).

Purchase, I...

Threshold methods should be used in risk assessment for genotoxic carcinogens, IUTOX newsletter July 1998, pp. 20-21.

Stellman, S.D.,

Cigarette yield and cancer risk: Evidence from case-control and prospective studies. in: International Agency for Research on Cancer (IARC) Scientific Publications No. 74, Tobacco: A major international health hazard (Zaridze, D.G., and Peto, R., eds.), p.187, Lyon, 1986,

Stubbe, I., Eskilsson, J., and Nilsson-Ehle, P.,

High-density lipoprotein concentrations increase after stopping smoking.

Br. Med. J. 284: 1511-1513 (1982)

U.S. Department of Health and Human Services (DHHS),

The Health Consequences of Smoking for Women, a report of the Surgeon General, Rockville, MD, 1980.

U.S. Department of Health and Human Services (DHHS).

The Health Consequences of Smoking, Cancer, a report of the Surgeon General, Rockville, MD. 1982.

U.S. Department of Health and Human Services (DHHS),

The Health Consequences of Smoking, Cancer, a report of the Surgeon General, Rockville, MD. 1982.

U.S. Department of Health and Human Services (DHHS), The Health Consequences of Smoking, Cardiovascular Disease, a report of the Surgeon General, Rockville, MD, 1983.

U.S. Department of Health and Human Services (DHHS), The Health Consequences of Smoking, Chronic Obstructive Lung Disease, a report of the Surgeon General, Rockville, MD, 1983.

U.S. Department of Health and Human Services (DHHS), Reducing the Health Consequences of Smoking, 25 Years of Progress, a report of the Surgeon General, Rockville, MD, 1989.

Zencik, H., and Bogdanffy, M.S., Harmonization of cancer and non-cancer risk assessment: moving beyond the NRC book, The Toxicologist 54: 194 (2000).